

## PATENT COOPERATION TREATY

REC'D 02 MAR 2005

## PCT

WIPO PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY  
(Chapter II of the Patent Cooperation Treaty)

## (PCT Article 36 and Rule 70)

Applicant's or agent's file reference 664182	<b>FOR FURTHER ACTION</b>		See Form PCT/IPEA/416
International application No. PCT/JP2004/000617	International filing date (day/month/year) 23.01.2004	Priority date (day/month/year) 24.01.2003	
International Patent Classification (IPC) or national classification and IPC C07D487/04, C07D519/00, A61K31/519, A61P1/00, A61P25/00			
Applicant TANABE SEIYAKU CO., LTD.			
<p>1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 9 sheets, including this cover sheet.</p> <p>3. This report is also accompanied by ANNEXES, comprising:</p> <ul style="list-style-type: none"> <li>a. <input type="checkbox"/> sent to the applicant and to the International Bureau) a total of sheets, as follows:           <ul style="list-style-type: none"> <li><input type="checkbox"/> sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).</li> <li><input type="checkbox"/> sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.</li> </ul> </li> <li>b. <input type="checkbox"/> (sent to the International Bureau only) a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).</li> </ul>			
<p>4. This report contains indications relating to the following items:</p> <ul style="list-style-type: none"> <li><input checked="" type="checkbox"/> Box No. I Basis of the opinion</li> <li><input checked="" type="checkbox"/> Box No. II Priority</li> <li><input checked="" type="checkbox"/> Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</li> <li><input checked="" type="checkbox"/> Box No. IV Lack of unity of invention</li> <li><input checked="" type="checkbox"/> Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</li> <li><input type="checkbox"/> Box No. VI Certain documents cited</li> <li><input type="checkbox"/> Box No. VII Certain defects in the international application</li> <li><input type="checkbox"/> Box No. VIII Certain observations on the international application</li> </ul>			
Date of submission of the demand 03.06.2004	Date of completion of this report 28.02.2005		
Name and mailing address of the international preliminary examining authority: European Patent Office - Gitschner Str. 103 D-10958 Berlin Tel. +49 30 25901 - 0 Fax: +49 30 25901 - 840	Authorized Officer  Hoepfner, W Telephone No. +49 30 25901-337		



**INTERNATIONAL PRELIMINARY REPORT  
ON PATENTABILITY**

International application No.  
PCT/JP2004/000617

**Box No. I Basis of the report**

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.
  - This report is based on translations from the original language into the following language, which is the language of a translation furnished for the purposes of:
    - international search (under Rules 12.3 and 23.1(b))
    - publication of the international application (under Rule 12.4)
    - international preliminary examination (under Rules 55.2 and/or 55.3)
2. With regard to the **elements\*** of the international application, this report is based on (*replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report*):

**Description, Pages**

1-291 as originally filed

**Claims, Numbers**

1-22 as originally filed

- a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3.  The amendments have resulted in the cancellation of:
  - the description, pages
  - the claims, Nos.
  - the drawings, sheets/figs
  - the sequence listing (*specify*):
  - any table(s) related to sequence listing (*specify*):

4.  This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

- the description, pages
- the claims, Nos.
- the drawings, sheets/figs
- the sequence listing (*specify*):
- any table(s) related to sequence listing (*specify*):

\* If item 4 applies, some or all of these sheets may be marked "superseded."

**INTERNATIONAL PRELIMINARY REPORT  
ON PATENTABILITY**

International application No.  
PCT/JP2004/000617

**Box No. II Priority**

1.  This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:
  - copy of the earlier application whose priority has been claimed (Rule 66.7(a)).
  - translation of the earlier application whose priority has been claimed (Rule 66.7(b)).
2.  This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rule 64.1). Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.
3. Additional observations, if necessary:

**Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:
  - the entire international application,
  - claims Nos. 19-22 (with respect to industrial applicability)  
because:
    - the said international application, or the said claims Nos. 19-22 relate to the following subject matter which does not require an international preliminary examination (specify):  
**see separate sheet**
    - the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
    - the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
    - no international search report has been established for the said claims Nos.
    - the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	<input type="checkbox"/> has not been furnished
	<input type="checkbox"/> does not comply with the standard
the computer readable form	<input type="checkbox"/> has not been furnished
	<input type="checkbox"/> does not comply with the standard
    - the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.
    - See separate sheet for further details

# INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.  
PCT/JP2004/000617

---

## Box No. IV Lack of unity of invention

---

1.  In response to the invitation to restrict or pay additional fees, the applicant has:
  - restricted the claims.
  - paid additional fees.
  - paid additional fees under protest.
  - neither restricted nor paid additional fees.
2.  This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is
  - complied with.
  - not complied with for the following reasons:  
**see separate sheet**
4. Consequently, this report has been established in respect of the following parts of the international application:
  - all parts.
  - the parts relating to claims Nos. .

---

## Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

---

### 1. Statement

Novelty (N)	Yes:	Claims	1-22
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-22
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-18
	No:	Claims	

### 2. Citations and explanations (Rule 70.7):

**see separate sheet**

**INTERNATIONAL PRELIMINARY  
REPORT ON PATENTABILITY  
(SEPARATE SHEET)**

International application No.

PCT/JP2004/000617

**Re Item III**

**Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

Claims 19-22 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, the International Examination Authority fully concurs with the objection put forward by the International Search Authority and no opinion will be formulated with respect to the industrial applicability of the subject-matter of this/these claims (Article 34(4)(a)(I) PCT).

**Re Item IV**

**Lack of unity of invention**

The International patent application WO-A-02079189 (D1) discloses SK channel-blocking compounds which structurally differ in the kind of substituent at position 4 of the piperazine moiety (see also paragraph "novelty" below) and their use in pharmaceutical compositions. These compounds have in common the same structural feature as the compounds of formula (I) of the present claim 1, namely a 1-((hetero)arylalkylene)-4-(piperazin-1-yl)-1H-pyrazolo[3,4-d]pyrimidine.

Hence, the distinguishing feature between the said compounds of formula (I) and the said compounds of D1 has to be seen as the particular kind of substituent at position 4 of the piperazine moiety, namely

$R^1-(O)_q-Y-Z-$  with  $R^1=(A)$  and  $Z=-CO-$ ;  
 $R^1-(O)_q-Y-Z-$  with  $R^1=(B)$  and  $Z=-CO-$ ;  
 $R^1-(O)_q-Y-Z-$  with  $R^1=(C)$  and  $Z=-CO-$ ;  
 $R^1-(O)_q-Y-Z-$  with  $R^1=(D)$  and  $Z=-CO-$ ;  
 $R^1-(O)_q-Y-Z-$  with  $R^1=(E)$  and  $Z=-CO-$ ;  
 $R^1-(O)_q-Y-Z-$  with  $Z=-CH_2-$ ;  
 $R^1-(O)_q-Y-Z-$  with  $Z=-SO_2-$ ; and  
 $R^1-(O)_q-Y-Z-$  with  $Z=C(=N-CN)-$ .

However, with the presence of 8 different distinguishing features and with the umbrella of any common structural feature being lost, the subject-matter of the present claim 1 can no longer be regarded as being unitarian and is therefore split into 8 different inventions (non-

**INTERNATIONAL PRELIMINARY  
REPORT ON PATENTABILITY  
(SEPARATE SHEET)**

International application No.  
**PCT/JP2004/000617**

unity a posteriori), the said inventions being as follows:

**INTERNATIONAL PRELIMINARY  
REPORT ON PATENTABILITY  
(SEPARATE SHEET)**

International application No.

PCT/JP2004/000617

- provision of a compound of formula (I) having a residue  $R^1-(O)_q-Y-Z-$  with  $R^1=(A)$  and  $Z=-CO-$  (invention #1);
- provision of a compound of formula (I) having a residue  $R^1-(O)_q-Y-Z-$  with  $R^1=(B)$  and  $Z=-CO-$  (invention #2);
- provision of a compound of formula (I) having a residue  $R^1-(O)_q-Y-Z-$  with  $R^1=(C)$  and  $Z=-CO-$  (invention #3);
- provision of a compound of formula (I) having a residue  $R^1-(O)_q-Y-Z-$  with  $R^1=(D)$  and  $Z=-CO-$  (invention #4);
- provision of a compound of formula (I) having a residue  $R^1-(O)_q-Y-Z-$  with  $R^1=(E)$  and  $Z=-CO-$  (invention #5);
- provision of a compound of formula (I) having a residue  $R^1-(O)_q-Y-Z-$  with  $Z=-CH_2-$ , (invention #6);
- provision of a compound of formula (I) having a residue  $R^1-(O)_q-Y-Z-$  with  $Z=-SO_2-$  (invention #7); and
- provision of a compound of formula (I) having a residue  $R^1-(O)_q-Y-Z-$  with  $Z=-C(=N-CN)-$  (invention #8).

**Re Item V**

**Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

D1: WO 02/079189 A (TANABE SEIYAKU CO ; TAKAMURO IWAO (JP); HOMMA KOICHI (JP); ISHIDA AKIH) 10 October 2002 (2002-10-10)

**Novelty**

The document D1, which is in fact assigned to the assignee of the present application, discloses SK channel-blocking compounds of formula (I-h) which structurally differ in the kind of substituent at position 4 of the piperazine moiety (see page 1, line 5; page 3, formula (I); page 22, formula (I-h); page 27, formulae; page 39, lines 10-16; Examples).

Consequently, novelty has to be acknowledged for the subject-matter of the present independent claims 1, 13, 18 and 19 and the present dependent claims 2-12, 14-17 and 20-22.

**INTERNATIONAL PRELIMINARY  
REPORT ON PATENTABILITY  
(SEPARATE SHEET)**

International application No.

PCT/JP2004/000617

**Inventive step**

For each of the 8 different inventions underlying the novel subject-matter, the distinguishing feature with respect to D1 has to be seen in the particular kind of substituent at the piperazine moiety as being outlined under item V above.

In the absence of any evidence for an unexpected technical effect linked to these features, the objective problem underlying each of these 8 inventions can merely be regarded as the provision of further SK channel-blocking agents.

However, since the 8 different solutions to this very general problem, namely the modification of the compounds of D1 by replacing the spiroisoquinoline residue with one of the 8 particular substituents as being outlined under item V above, was not foreshadowed in the prior art, the presence of inventive activity has to be acknowledged for each of the said solutions, even in the absence of a technical effect.

**Industrial applicability**

There is no doubt that the subject-matter of the present claims 1-18 is industrially applicable.

However, for the assessment of the present claims 19-22 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

**Formal matters, clarity**

Although in the present claims terms such as "aryl", "heteroaryl" and the like are clear as such, they introduce obscurity in that they unduly extend the scope of the claimed subject-matter (breadth of the claims).

Consequently, the said terms should either be deleted or at least rendered more precise by appropriate limitation, provided there can be found sufficient support for this in the description.

**INTERNATIONAL PRELIMINARY  
REPORT ON PATENTABILITY  
(SEPARATE SHEET)**

International application No.

**PCT/JP2004/000617**

The following expressions lack clarity:

"Lower" alkyl and the like.

"Cyclo-lower alkyl group" (claim 1).

"Substituted".